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PATENT
2801-0155

#27
10/4/01

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of		Before the Board of Appeals	
Susan M. DALUGE et al.		Appeal No.:	
Appl. No.:	08/957,045	Group:	1624
Filed:	October 24, 1997	Examiner:	M. BERCH
Conf.:			
For:	CHLOROPYRIMIDINE INTERMEDIATES		

APPEAL BRIEF TRANSMITTAL FORM

Assistant Commissioner for Patents
Washington, D.C. 20231:

September 27, 2001

Sir:

Transmitted herewith is an Appeal Brief (in triplicate) on behalf of the Appellants in connection with the above-identified application.

☐ The enclosed document is being transmitted via the Certificate of Mailing provisions of 37 C.F.R. 1.8.

A Notice of Appeal was filed on June 1, 2001.

☐ Applicant claims small entity status in accordance with 37 C.F.R. § 1.27

The fee has been calculated as shown below:

☒ Extension of time fee pursuant to 37 C.F.R. §§ 1.17 and 1.136(a) - $390.00 - two (2) months (large entity)

☒ Fee for filing an Appeal Brief - $310.00 (large entity).

☒ A check in the amount of $700.00 is attached.

☐ Please charge Deposit Account No. 02-2448 in the amount of $0.00. A triplicate copy of this sheet is attached.

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If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

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(Rev. 01/22/01)

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BRIEF ON BEHALF OF APPELLANTS

Honorable Commissioner for Patents
Washington, DC 20231

September 27, 2001

Sir:

This is an Appeal from the Final Rejection of claims 9 and 18-22 in the above-identified application, in which the claims were finally rejected in the Office Action mailed December 1, 2001.

I. REAL PARTY IN INTEREST

This application is assigned to GlaxoWellcome Inc. Due to a corporate merger, the application is now owned by SmithKline Beecham Corporation. The assignment of the application to GlaxoWellcome, Inc. was recorded on July 31, 1996 at Reel 8173, Frame 0572.

II. RELATED APPEALS AND INTERFERENCES

No related appeals or interferences are pending.

III. STATUS OF THE CLAIMS

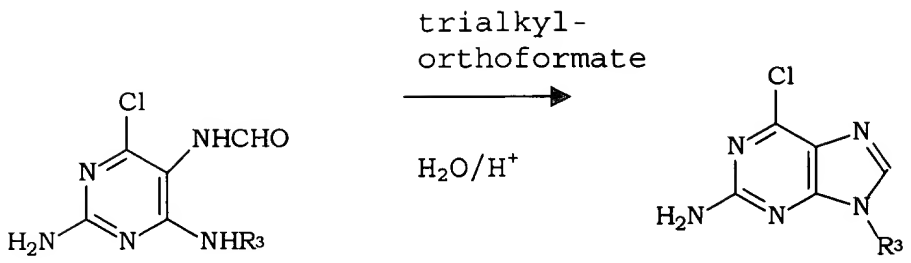
The Examiner has finally rejected claims 9 and 18-22. Claims 9 and 18-22 are set forth in the attached Appendix. The rejection of claims 9 and 18-22 are hereby appealed.

IV. STATUS OF THE AMENDMENTS

The Examiner asserted in the Advisory Action mailed May 23, 2001, that the Amendment After Final filed May 1, 2001 would be entered upon timely submission of a Notice of Appeal and Appeal Brief.

V. SUMMARY OF THE INVENTION

As described in the claims, the present invention is directed to a process for the preparation of the compound of formula (VII). The process comprises reacting a compound of the formula (VI) with a trialkylorthoformate in the presence of an aqueous acid. The reaction scheme is depicted below.



(VI) (VII)

The present inventive process has significant advantages over the cited prior art. The present inventive process has made it possible to synthesize the desired compound of formula (VII) in large quantities with little need for purification.

VI. ISSUES

1. Claims 9 and 18-22 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The Examiner identified five issues in the Office Action mailed December 1, 2001; however, the Examiner stated in the Advisory Action mailed May 23, 2001 that issue number four was resolved by the Response filed May 1, 2001.

2. Claims 9 and 18-22 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Daluge '697 (USP 5,087,697) in view of Vince '224 (USP 4,916,224) or Daluge '671 (USP 5,049, 671), further in view of Norbeck '703 (USP 4,988,703), Vince

'607 (USP 5,736,607), Bothwick '531 (4,857,531) or Shealy '736 (USP 4,728,736).

3. Claims 9 and 18-22 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Norbeck '703, Vince '607, Bothwick '531 or Shealy '736 in view of EP '544 or Daluge '697.

Therefore, two main issues remain for argument. First, the alleged indefiniteness of certain terms within the claim language and whether claims 9 and 18-22 are obvious in view of the cited prior art.

VII. GROUPING OF CLAIMS

The Honorable Board of Patent Appeals and Interferences is requested to give separate consideration to the groups of claims identified below.

35 U.S.C. §112 Issues

Group I - Claims 9, 18 and 21-22, Issue 1

Group II - Claims 19 and 20, Issue 1

35 U.S.C. §103(a) Issues

Group III - Claims 9 and 18-22, Issues 2 and 3

VIII. ARGUMENTS

Group I - Issues under 35 U.S.C. §112

Claims 9, 18, 21 and 22 stand rejected under 35 U.S.C. §112, second paragraph as being indefinite. The Examiner has identified five terms or phrases that he alleges are indefinite. Appellants' item numbers below correspond to the item numbers in the Office Action mailed December 1, 2001.

1. Glycosidic Bond

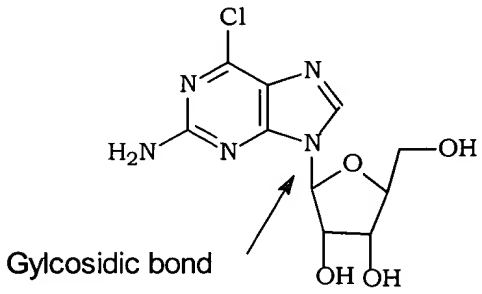
The Examiner has taken the position that the term "glycosidic bond" is unclear, because there is no generally accepted definition for glycosides. The Examiner has consistently argued that "glycosidic bond" is not defined in the specification and a skilled artisan would not understand the phrase. "Thus, for instance, the specification informs but does not control, the claim construction. Rather, in that process, the claim language itself governs the meaning of the claim. To acquire proper context to understand claim terms, this court also consults the specification, the prosecution history, and where relevant (and not contradictory of intrinsic evidence), extrinsic evidence." Envirco Corp. v. Clestra Cleanroom, Inc., 54 U.S.P.Q.2d 1449, 1453 (Fed. Cir. (2000), *citing,* Pitney

Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1308-09, 51 USPQ2d 1161, 1167-68 (Fed. Cir. 1999).

Appellants have produced a prosecution history that describes the phrase "glycosidic bond" and have attached photocopies from "Organic Chemistry" by G. Marc Loundon (Exhibit A), which is a college sophomore organic chemistry text from 1988 that has defined a "glycosidic bond." The organic chemistry text on page 1212 defines glycosides as "special types of acetals in which one of the oxygens of the acetal linkage is the ring oxygen of the pyranose or furanose." On pages 1229 and 1230 of the organic chemistry text, the text indicates a "glycosidic linkage" between two carbohydrates. "It is appropriate to compare the meaning of terms given in technical dictionaries in order to ascertain the accepted meaning of a term in the art." MPEP §2173(a), *citing* In re Barr, 444 F.2d 588, 170 U.S.P.Q. 330 (CCPA 1971). "Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification." MPEP §2173.05(b).

Appellants use the term "glycosidic bond" to describe or define the same bond described in the Organic Chemistry text, except the bond in the instant application is a special type of unstable "aminal linkage" in which the oxygen of the aminal is

the ring oxygen of a pyranose or furanose. The following diagram indicates a glycosidic bond.



The glycosidic bond is the bond between the "exemplary" ribose moiety and the purine moiety of the above compound. The ribose moiety is exemplary of an excluded R^3 group bound through a "glycosidic bond."

Appellants have excluded such compounds from R^3 by use of the phrase "provided that such groups are not attached by a glycosidic bond." The exclusion is required because of the instability of such chemical bonds. The nitrogen atom of the purine compound bound to a carbon atom that is bound to an oxygen atom as described above provides an unstable linkage. This structure is an aminal and the aminal will "open up" in the harsh conditions the reaction. A skilled artisan would understand this relationship between the purine nitrogen of the present invention and compounds that form such an acetal. Therefore, the entire scope of the variable R^3 is clear to a skilled artisan.

The Examiner appears to be confusing the matter by discussing the metes and bounds of what is a glycoside or all variations thereof. It is a simple aminal linkage that Appellants are concerned with and have defined it accordingly. If a compound forms such an aminal linkage, glycosidic bond, when bound to the purine, the compound is not within the scope of R^3. It does not matter what the rest of the molecule has on it or whether the Examiner considers the molecule a sugar or not. Appellants have defined the excluded bond with clarity that allows a skilled artisan to understand the molecules within the scope of R^3.

2. Acyclic Group

The Examiner maintains that the phrase "acyclic group, wherein such acyclic group may be optionally substituted . . ." in the context of claims 9, 18, 21 and 22 is internally inconsistent. The Examiner alleges that an acyclic group already allows substitution; thus Appellants' language reciting optional substitutions is redundant. The Examiner alleges that it is unclear as to the purpose of the list of substitutions.

"[A] patentee is free to be his own lexicographer." Hormone Research Foundation Inc. v. Genetech Inc., 904 .2d 1558, 15 U.S.P.Q.2d 1039 (Fed. Cir. 1990). "Examiners are encouraged to suggest claim language used, but should not reject claims or

insist on their own preferences if other modes of expression selected by applicants satisfy the statutory requirement." MPEP §2172.02.

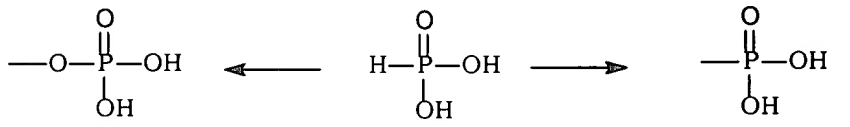
Clearly, Appellants mean for the optional list of substituents to guide a skilled artisan to the substitutions on the acyclic group. Appellants assert the language is clear and definite and satisfies the statutory requirements.

3. Phosphonyl

The Examiner and Appellants have come to an impasse as to the meaning of a "phosphonyl group." The Examiner continues to try to impose carbonyl nomenclature onto a phosphorous system without any support for his assertions. The Examiner maintains that $-P(O)(OH)_2$ is a "phosphoryl" group. Appellants assert that the term "phosphonyl" is the correct term for the group $-P(O)(OH)_2$.

Appellants have attached photocopies of pages from "Comprehensive Organic Chemistry: Volume 2 Nitrogen Compounds, Carboxylic Acids, Phosphorous Compounds" (Exhibit B). Starting on page 1122 of the 1979 reference, the nomenclature of phosphorous compounds is described as "the most frustrating exercise for most chemists." "Phosphonyl" is a term used to describe a group having three oxygens bound to phosphorus. "Phosphoryl" is a term used to describe a group having four

oxygens bound to phosphorus. "Phosphinyl" is a term used to describe a group having two oxygens bound to phosphorus. See below.



The Examiner is correct in that a phosphonic acid has three oxygens bound to a phosphorous atom, but the Examiner confuses the matter by stating "[h]ence, phosphonyl would be the acyl of this, formed by removal of the OH to give RP(O)(OH)-." This is incorrect. It would become a phosphinic group. *See Chapter 10.5 of "Comprehensive Organic Chemistry: Volume 2 Nitrogen Compounds, Carboxylic Acids, Phosphorous Compounds" on page 1257.*

The structure above on the right is a phosphonyl group. It has three oxygens bound to a phosphorous atom with an additional substituent. Phosphoryl has four oxygens bound to a phosphorous atom. The moiety described by the Examiner only has two oxygens bound to the phosphorous atom. This moiety is a phosphinic group.

Appellants assert that a skill artisan would understand the term "phosphonyl" to mean a group with three oxygens bound to phosphorous, as described above.

4. C_{3-7} carbocyclic group

The Examiner has raised concerns that the term "group" in the phrase "C_{3-7} carbocyclic group" is indefinite. The Examiner alleges that the scope of the phrase "C_{3-7} carbocyclic group" is unclear to a skilled artisan. The Examiner suggests amending the claims language to "C_{3-7} carbocycle."

The claim language reads "a C_{3-7} carbocyclic group, optionally substituted with substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or protected hydroxyl, azido, phosphonyl, and halogen." Appellants assert that a skilled artisan reading the above limitation in context would understand "C_{3-7} carbocyclic group" to be the cyclic group and the following listed substituents to be substituted on the carbocyclic group.

The Examiner is concerned that "C_{3-7} carbocyclic group" is allegedly indefinite because it might be construed as containing a "benzyl group" is unwarranted and outside the context of the instant specification and claims. The Examiner asserts that the term "group" is ambiguous. Appellants traverse this interpretation of the language of the present claims.

In the context of the claim as interpreted in light of the specification, a skilled artisan would understand "a C_{3-7} carbocyclic group, optionally substituted" as a C_{3-7} carbocycle with optional substitution. Appellants have clearly defined this meaning by the context surrounding the alleged indefinite phrase. The term "group" does not add confusion as alleged by the Examiner.

Group II - Issues under 35 U.S.C. §112

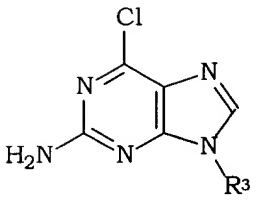
Claims 19-20 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

Claims 19 and 20 specifically describe the substituents that define the scope of variable R^3. The alleged indefinite terms are all related to the scope of the variable R^3. Therefore, claims 19 and 20 are free of the alleged indefinite terms or phrases and should not be rejected under 35 U.S.C. §112, second paragraph.

GROUP III - ISSUE UNDER 35 U.S.C. § 103(a)

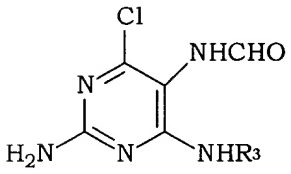
Present Invention and Advantages

The present invention is directed to a process for the preparation of a compound of formula (VII)



(VII)

comprising reacting a compound of formula (VI)



(VI)

with a trialkylorthoformate in the presence of an aqueous acid.

This synthetic step is an important step in the total synthesis of the oral nucleoside reverse transcriptase inhibitor marketed under the trademark Ziagen®, namely, (1S,cis)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol. Carbocyclic nucleosides have inspired a great deal of innovative synthesis since Shealy and Clayton's first report of racemic carbocyclic adenosine. *J. Am. Chem. Soc.*, 1966, 88, 3885-3887; 1969, 91, 3075-3083. However, syntheses were based only on research quantities; thus, the synthetic schemes only produced small amounts. To produce the drug Ziagen®, a larger scale synthesis was urgently needed and the instant synthetic step is

part of a scheme to synthesize a carbocyclic nucleoside on a metric ton scale.

The synthetic step of cyclization of compounds of formula VI into compounds formula VII as defined in the claims occurs smoothly in aqueous acid in 85-93% yield.

ISSUE 2

Claims 9 and 18-22 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Daluge '697 (USP 5,087,697) in view of Vince '224 (USP 4,916,224) or Daluge '671 (USP 5,049, 671), further in view of Norbeck '703 (USP 4,988,703), Vince '607 (USP 5,736,607), Bothwick '531 (4,857,531) or Shealy '736 (USP 4,728,736).

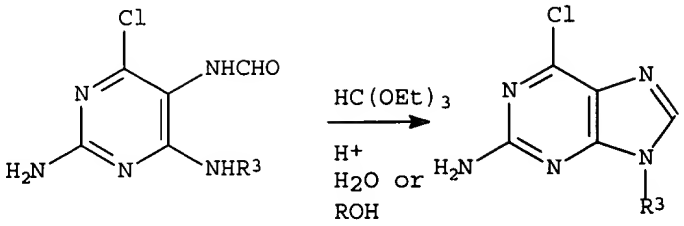
Patentable Distinctions Between the Present Invention and Daluge '697 in view of Vince '224 or Daluge '671, further in view of Norbeck '703, Vince '607, Bothwick '531 or Shealy '736

Lack of *Prima Facie* Case of Obviousness

Daluge '697 discloses a process of producing 6-substitued purine carbocyclic nucleosides. Daluge '697 and Daluge '671 disclose synthetic pathways to make carbocyclic nucleosides. Specifically in Daluge '697, two processes are described that use cyclization steps to make a purine attached to a carbocycle

via a nitrogen atom. The present Inventive Process and Route 1 and Route 2 as described in Daluge '697 are illustrated below.

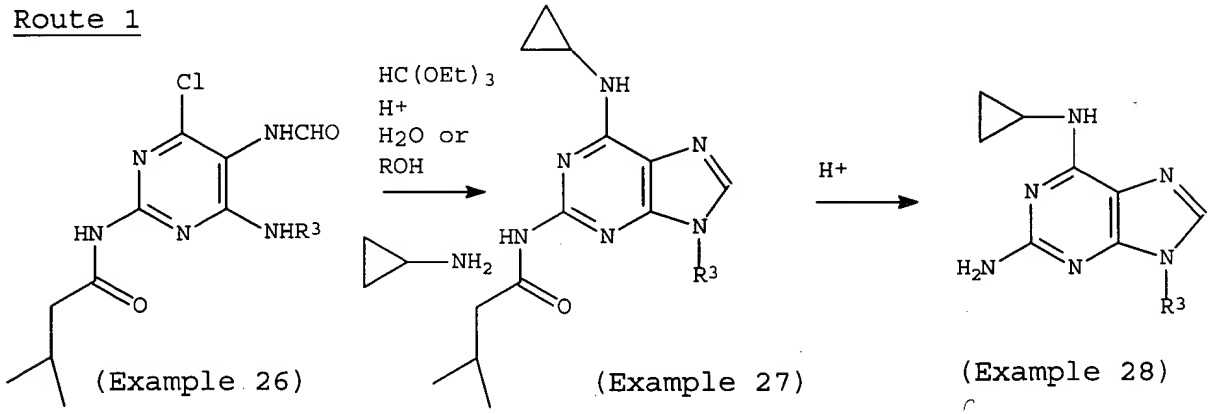
Present Inventive Process



(VI) (VII)

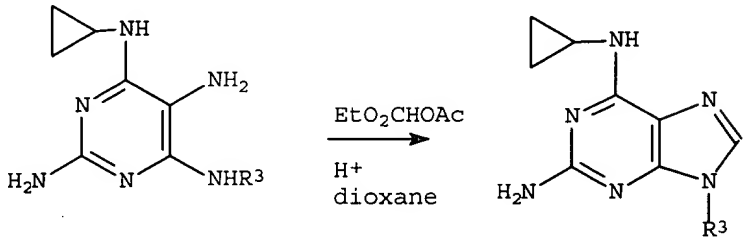
Daluge '697 Processes

Route 1



(Example 26) (Example 27) (Example 28)

Route 2



(Example 3) (Example 4)

Neither of the two processes described by Daluge '697 use a compound which is the same as the compound of formula (VI) to make the compound of formula (VII). Route 1 described above protects every amine, which results in an additional step to remove the protecting group. Route 2 described above does not protect either amino position and does not have a chlorine substituent and has a yield below 50%.

Vince '224 discloses a preparation of a carbocyclic nucleoside. Vince '224 discloses a triaminopyrimidine intermediate, (6b), which is air- and light-sensitive and extremely hard to purify. The cyclization step provides a low yield that requires extensive purification.

Norbeck '703 discloses a compound that has two unprotected amino groups at positions 2 and 5 of the pyrimidine ring. Norbeck '703 discloses in Example 1, step G (column 19), a synthetic step that produces three compounds, which need column chromatography to separate them. This is a similar synthetic step as Route 2 of Daluge '697 and has the same low yield.

Borthwick '531 discloses the preparation of carbocyclic purines. Example 15 of Borthwick '531, (columns 17 and 18) discloses an intermediate containing an unprotected amino group at position 2 of the pyrimidine ring, but the described synthetic step results in a "sticky foam" and a "red filtrate."

Therefore, the Borthwick '531 cyclization step teaches unsatisfactory result with a contaminated low yield.

Shealy '736 discloses the preparation of carbocyclic purines. In the Example 1 of Shealy '736, pyrimidine V has two unprotected amino groups at positions 2 and 5 of the pyrimidine ring and the resulting cyclized product is a "red syrup" in a yield of 52%. Shealy '736 describes extensive purifying procedures to isolate the desired carbocyclic purine in low yield. Again, this Shealy '736 synthetic step describes unsatisfactory results similar to route 2 of Daluge '697.

Vince '607 discloses a synthetic pathway to carbocyclic purines using a pyrimidine intermediate with unprotected amino groups at position 2 and 5 of the pyrimidine ring. As described in the above-cited references, the Vince '607 synthetic step teaches a requirement for extensive purification procedures to isolate the desired carbocyclic purine in low yield.

The Examiner continues to maintain that the prior art renders obvious the claimed cyclization reaction, because the prior art discloses cyclization reactions with both protected and unprotected amino groups on the pyrimidine ring. The Examiner has continued to ignore the fact the synthetic steps disclosed in the cited prior art have remarkably low yields and contaminated products. More importantly, none of the cited prior art disclose a starting pyrimidine with an unprotected

amino group at the 2 position, a formyl protected amino group at the 5 position and a chlorine at the 4 position.

The prior art of record shows that cyclization steps with unprotected amines results in low yield "dark red syrups" and low yield "sticky foams" and "red filtrates" that are unsuitable for large scale manufacturing of product, which explains why Daluge '697 uses the doubly protected compound in Route 1 described above. *See Examples 3 and 4 of Daluge '697.*

In order to make a proper *prima facie* case of obviousness, the prior art must suggest the invention. The motivation to combine the references must come from the prior art itself, In re Dembiczak, 175 F.3d 994, 50 U.S.P.Q.2d (BNA) 1614 (Fed. Cir. 1999) and In re Rouffet, 149 F.3d 1350, 47 U.S.P.Q.2d (BNA) 1453 (Fed. Cir. 1998).

> [T]herefore an examiner may often find every element of the claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability."

In re Roufett, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1458 (Fed. Cir. 1998), *quoting* Sensonics, Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570, 38 U.S.P.Q.2d 1551, 1554 (Fed. Cir. 1996).

In the instant application, Appellants achieved a breakthrough synthesis of carbocyclic purines by arranging the substituents in a precise manner as described in Formula (VI). The cited references never recognize this claimed arrangement. Therefore, a skilled artisan would not be motivated to combine the references as assumed by the Examiner. Therefore, the Examiner has not presented a *prima facie* case of obviousness and the present claims are allowable over the cited references.

Unexpected Results

Alternatively, if the Board holds that a *prima facie* case of obviousness has been established, Applicants submit that such *prima facie* case of obviousness has been rebutted by the unexpected superior results set forth in the Declaration (Exhibit C). Appellants submitted a 37 C.F.R. §1.132 Declaration from Dr. Susan M. Daluge on May 1, 2001. Dr. Daluge is an inventor of the present application and an inventor of Daluge '697. Dr. Daluge explains in the Declaration that removing the amino protecting group at an earlier step resulted in side-reactions that reduced the yield in three important steps. Furthermore, Dr. Daluge explains that the reactions without the amine protecting group resulted in tars, which are problematic as intermediate products in a total synthesis.

The Declaration provides testimony that a skilled artisan would not be motivated to use a compound of formula VI, because a skilled artisan would expect side-reactions that persisted in Example 4 of Daluge '697, which hampered purification and reduced yield. In Example 8, page 21 of the present invention, Appellants achieved a 92% yield of a purine product. This is unexpectedly superior to the purine product disclosed Daluge '697 and Daluge '671 in Example 4, column 13, and column 11, respectively, which has a 46% yield. A 46% yield for the final step of a synthesis in a manufacturing process is unacceptable to a skilled artisan. Thus, a skilled artisan would not have a expected such superior results.

The secondary references fail to add any motivation to change the synthetic pathways described by Daluge '697. Norbeck '703, Vince '607, Bothwick '531 and Shealy '736 all use slight variations of Route 2 in Daluge '697. The secondary references describe the cyclization step without a protecting group on the amino substituent. The yields and products described in the secondary references are similar to the yield and product described in Daluge '697, i.e., low yield "dark red syrups" and low yield "sticky foams" and "red filtrates", which are unsuitable for large scale manufacturing of product.

Dr. Daluge is the inventor of the present invention as well as the inventor of the primary reference used as the closest

prior art. Applicants agree that Daluge '697 is the closest prior art, especially since the other cited references use the same synthetic scheme Route 2 as described above.

In her §132 declaration, Dr. Daluge explains the side-by-side comparison of Example 4 in Daluge '697 and the present invention. However, the Examiner fails to accept this explanation by stating "[t]he declaration gives conclusions without the actual experiments to back them up." Appellants assert that the Examiner is not using proper U.S. patent procedure to evaluate the Declaration of Dr. Daluge. Patent rules do not require that the experiments be performed in the same time frame. Dr. Daluge was present at the time the experiments discussed were performed and signed under penalty of perjury that her declaration is true as to the results of the experiments.

Thus, regardless of the issues regarding prima facie obviousness, the present invention provides unexpected superior results as compared to prior processes and is, therefore, patentably distinct.

ISSUE 3

Claims 9 and 18-22 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Norbeck '703, Vince '607, Bothwick

'531 or Shealy '736 in view of EP '544 (EP 413,544) or Daluge '697.

Patentable Distinctions Between the Present Invention and Norbeck '703, Vince '607, Bothwick '531 or Shealy '736 in view of EP '544 or Daluge '697

Lack of Prima Facie Case of Obviousness

As discussed above, Norbeck '703, Vince '607, Bothwick '531 and Shealy '736 each disclose cyclization steps to make purines. Appellants have described above that none of Norbeck '703, Vince '607, Bothwick '531, or Shealy '736 disclose the claimed the compound of formula (VI). These references basically use the same procedure as described in Example 4 of Daluge '697.

Norbeck '703, Vince '607, Bothwick '531 and Shealy '736 each fail to suggest alone or in combination the substitution pattern present on the claimed compound of formula (VI). As stated above and throughout the present specification the claimed invention leads to unexpectedly high yields and exceptional purity.

As for the secondary reference EP '544, EP '544 fails to disclose or suggest the process of the present invention. EP '544 discloses a fundamentally different process using different reactants to achieve different final compounds. EP '544 fails

to provide any additional motivation to synthesize the desired compound of formula (VII) in large quantities with relatively minimal purification.

EP '544 and Daluge '697 fail to disclose the compounds of formula (VI) present in the present invention. The cited references reviewed in their entirety fail to disclose or suggest the inventive process.

The cited prior art fails to teach or suggest using a compound of formula VI as a starting material in the synthesis of a compound of formula VII. None of the references ever suggest, alone or in combination, a compound of formula (VI), wherein one amine group is not protected, a chlorine is present on the pyrimidine ring, one amino group has a formyl protecting group and the third amino group has a protecting group of a compound in the scope of R^3.

The Examiner must present a *prima facie* case of obviousness consisting of motivation or suggestion to modify or combine references such that one of ordinary skill in the art has a reasonable expectation of success of using the present process. "To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the

same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. In re Rouffet, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457-58 (Fed. Cir. 1998). Since the cited references fail to disclose a compound of formula VI as set forth in the claims, a *prima facie* case of obviousness has not been presented and the claims are patentable.

Unexpected Results

Alternatively, if the Board holds that a *prima facie* case of obviousness has been established, Applicants have rebutted any such obviousness rejection by the unexpected superior results achieved by the present invention as set forth in the previously submitted Declaration. As declared by Dr. Daluge, a skilled artisan would not expect such good yield in the cyclization of a compound of formula (VI).

The attached Declaration provides evidence that a skilled artisan would not expect success with the compounds of formula (VI) in the cyclization step to form compounds of formula (VII). A skilled artisan would not have been motivated to use the claimed process from reading the cited references as assumed by the Examiner. The teachings of the combined references fail to

suggest, individually or collectively, the superior results of the present invention.

Conclusion

The Honorable Board of Patent Appeals and Interferences is respectfully requested to reverse the rejections of the claims.

The required Appeals Brief fee in the amount of $310.00 is attached hereto.

Applicants petition under 37 C.F.R. §1.17 and 1.136(a) for filing a two (2) month extension of time for filing a response in connection with the present application. Thus, the required fee of $390.00 for a two (2) month extension of time is attached hereto.

If the Examiner has any questions regarding the above matters, please contact Applicants' representative, Mark W. Milstead (Reg. No. 45,825), in the Washington, metropolitan area at the telephone number listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any

additional fee required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Gerald M. Murphy, Jr.
Reg. No.: 28,977

P. O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

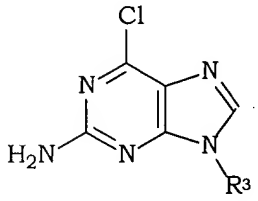
GMM/MWM/gml

Attachments: Appendix
Exhibits A, B, and C

APPENDIX

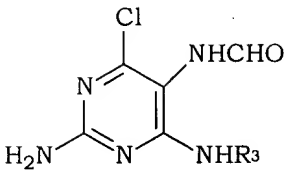
CLAIMS UNDER APPEAL

9. A process for the preparation of a compound of formula (VII)



(VII)

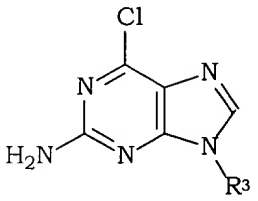
wherein R^3 is hydrogen; hydroxyl; a C_{3-7} carbocyclic group, optionally substituted with substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or protected hydroxyl, azido, phosphonyl, and halogen; an acyclic group, wherein such acyclic groups may be optionally substituted with substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or protected hydroxyl, azido, phosphonyl, and halogen; or a C_{4-7} heterocyclic group, wherein said C_{4-7} heterocyclic group has a one or more heteroatoms selected from the group consisting of a N, O and S atom and wherein such C_{4-7} heterocyclic group may be optionally substituted with substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or protected hydroxyl, azido, phosphonyl, and halogen; provided that such groups are not attached by a glycosidic bond, comprising reacting a compound of formula (VI)



(VI)

wherein R^3 is as defined above, with a trialkylorthoformate in the presence of an aqueous acid.

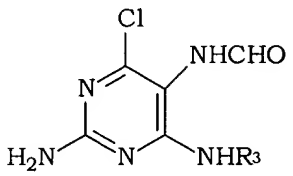
18. A process for the preparation of a compound of formula (VII)



(VII)

wherein R^3 is a C_{3-7} carbocyclic group, optionally substituted with substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or protected hydroxyl, azido, phosphonyl, and halogen; an acyclic group, wherein such acyclic group may be optionally substituted with substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or protected hydroxyl, azido, phosphonyl, and halogen; or a C_{4-7} heterocyclic group, wherein said C_{4-7} heterocyclic group has a one or more heteroatoms selected from the group consisting of a N, O and S atom and wherein such C_{4-7} heterocyclic group may be

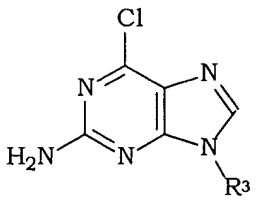
optionally substituted with substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or protected hydroxyl, azido, phosphonyl, and halogen; provided that such groups are not attached by a glycosidic bond, comprising reacting a compound of formula (VI)



(VI)

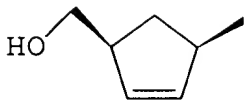
wherein R^3 is as defined above, with a trialkylorthoformate in the presence of an aqueous acid.

19. A process for the preparation of the compound of formula (VII)

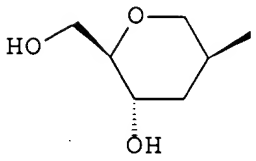


(VII)

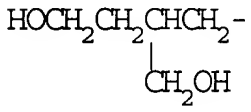
wherein R^3 is selected from:

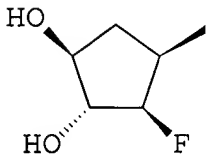
a.  ;

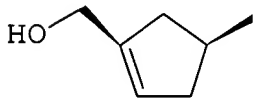
b. H;

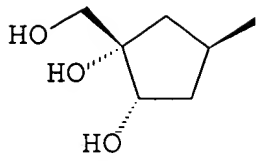
c.  ;

d. $\underline{(CH_3C(O)CH_2)}_2CHCH_2CH_2-$;

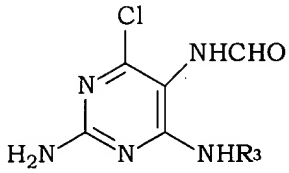
e.  ;

f.  ;

g.  ;and

h. 

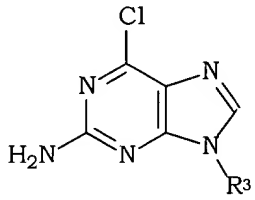
comprising reacting a compound of formula (VI)



(VI)

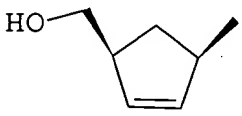
wherein R^3 is as defined above with a trialkylorthoformate in the presence of an aqueous acid.

20. A process for the preparation of a compound of formula (VII)

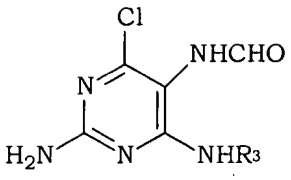


(VII)

wherein R^3 is



comprising reacting a compound of formula (VI)

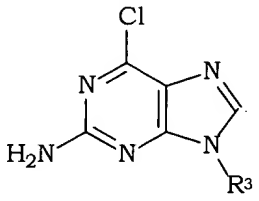


(VI)

wherein R^3 is as defined above with a trialkyorthoformate in the presence of an aqueous acid.

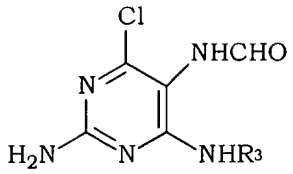
21. A process according to claim 9, wherein R^3 is a C_{3-7} carbocyclic group.

22. A process for the preparation of a compound of formula (VII)



(VII)

wherein R^3 is an acyclic group, wherein such acyclic group may be optionally substituted with substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or protected hydroxyl, azido, phosphonyl, and halogen; provided that such groups are not attached by a glycosidic bond, comprising reacting a compound of formula (VI)



(VI)

wherein R^3 is as defined above, with a trialkylorthoformate in the presence of an aqueous acid.

Organic Chemistry

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G. Marc Loudon
Purdue University

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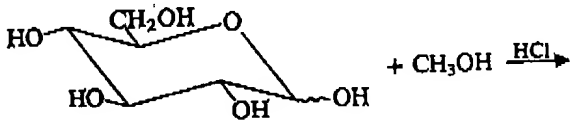
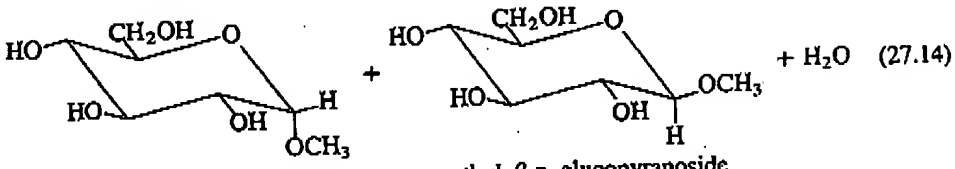
Problem **8** Into what aldose and 2-ketose would D-galactose first be transformed on treatment with base? Name the aldose (see Fig. 27.1) and give the structure of the ketose.

27.5 GLYCOSIDES

Most sugars react with alcohols under acidic conditions to yield cyclic acetals.



D-glucose

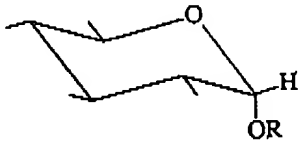


(27.14)

methyl α-D-glucopyranoside (83–85% yield; separated by fractional crystallization)

methyl β-D-glucopyranoside

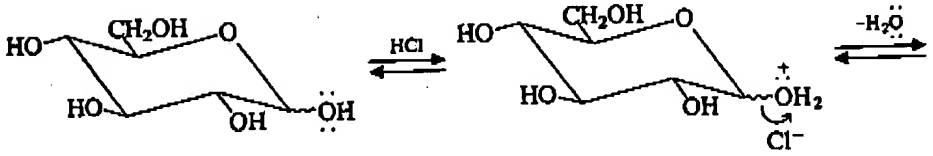
Such compounds are called **glycosides**. They are special types of acetals in which one of the oxygens of the acetal linkage is the ring oxygen of the pyranose or furanose.

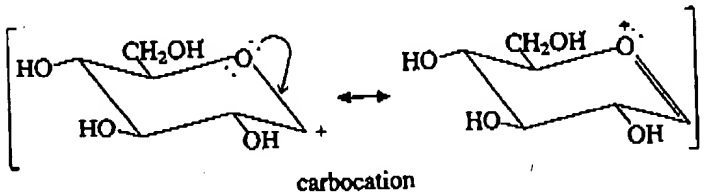


acetal linkage

As illustrated in Eq. 27.14, glycosides are named as derivatives of the parent sugar. The term *pyranoside* indicates that the glycoside ring is a six-membered ring. The term *furanoside* is used for a five-membered ring.

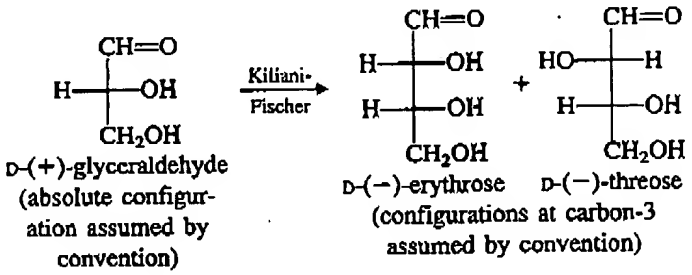
Glycoside formation, like acetal formation, is catalyzed by acid and involves carbocation intermediates.





(27.15a)

carbocation



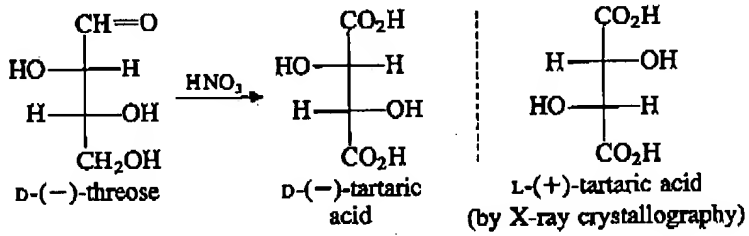
D-(+)-glyceraldehyde (absolute configuration assumed by convention)

D-(−)-erythrose D-(−)-threose (configurations at carbon-3 assumed by convention)

(27.46)

This sequence of reactions showed that (+)-glucose, (−)-erythrose, (−)-threose, and (+)-glyceraldehyde were all of the same stereochemical series—the D series. Oxidation of D-(−)-threose with dilute HNO_3 gave D-(−)-tartaric acid.

In 1950 the absolute configuration of naturally occurring (+)-tartaric acid (as its potassium rubidium double salt) was determined by a special technique of X-ray crystallography called *anomalous dispersion*. This determination was made by J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel, Dutch chemists who worked, appropriately enough, at the van't Hoff laboratory in Utrecht. If Fischer had made the right choice for the D configuration, the assumed structure for D-(−)-tartaric acid and the experimentally determined structure of (+)-tartaric acid determined by the Dutch crystallographers would be enantiomers. If Fischer had guessed wrong, the assumed structure for D-tartaric acid would be the same as the experimentally determined structure of L-tartaric acid, and would have to be reversed. To quote Bijvoet and his colleagues: *"The result is that Emil Fischer's convention* [for the D configuration] *appears to answer to reality."*



D-(−)-threose D-(−)-tartaric acid L-(+)-tartaric acid (by X-ray crystallography)

(27.47)

Problems

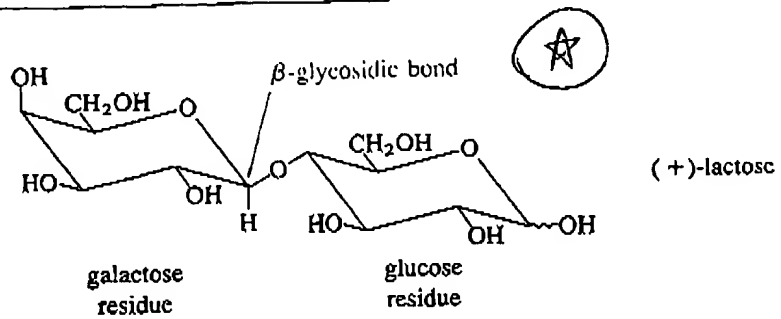
19 Given the structure of D-glyceraldehyde, how would you assign a structure to each of the two sugars obtained from it by Eq. 27.46, assuming that these compounds were previously unknown?

20 Suppose that a scientist were to reexamine the crystallographic work that established the absolute configuration of L-(+)-tartaric acid and finds that the structure of this compound was the mirror image of the one given in the text above. What changes would have to be made in Fischer's structure of D-(+)-glucose?

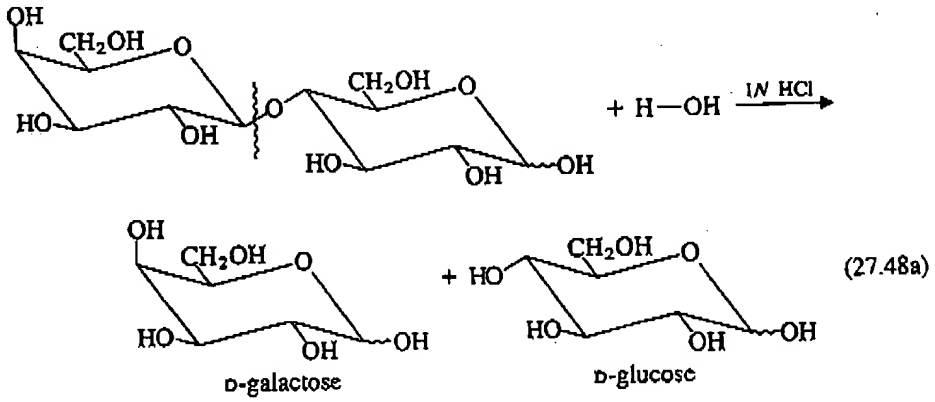
27.10 DISACCHARIDES AND POLYSACCHARIDES

A. Disaccharides

Disaccharides consist of two simple sugar residues, or *monosaccharides*, connected by a glycosidic linkage. (+)-Lactose is an example of a disaccharide. ((+)-Lactose is present to the extent of about 4.5% in cow's milk and 6–7% in human milk.)

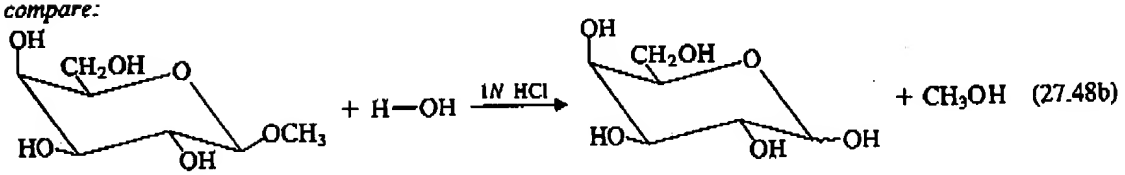


In (+)-lactose, a D-glucopyranose molecule is linked by its oxygen at carbon-4 to carbon-1 of D-galactopyranose. In effect, (+)-lactose is a glycoside in which galactose is the sugar and glucose is the "aglycone." As we have learned, the glycosidic linkage is an acetal, and therefore hydrolyzes under acidic conditions. Hence it is not surprising that (+)-lactose can be hydrolyzed in acidic solution to give one molecule each of D-glucose and D-galactose, in the same sense that a methyl glycoside can be hydrolyzed to give methanol and a sugar:



(27.48a)

compare:



(27.48b)

Certain enzymes also catalyze the same reaction at pH values near neutrality.

The stereochemistry of the glycosidic bond in (+)-lactose is β. That is, the stereochemistry of the oxygen linking the two sugar residues in the glycosidic bond corresponds to that in the β-anomer of D-galactopyranose. This stereochemistry is very important in biology, because higher animals possess an enzyme, β-galactosidase, that catalyzes the hydrolysis of this β-glycosidic linkage; this hydrolysis allows lactose to act as a source of glucose. α-Glycosides of galactose are inert to the action of this enzyme.

Because carbon-1 of the galactose residue in (+)-lactose is involved in a glycosidic linkage, it cannot be oxidized. However, carbon-1 of the glucose residue is part of a hemiacetal group, which, like the hemiacetal group, of monosaccharides, is in equilibrium with the free aldehyde, and can undergo characteristic aldehyde reactions. Thus, oxidation of (+)-lactose with bromine water (Sec. 27.7A) effects oxidation of the glucose residue:

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diatomic species P_2, PN, and PO are only observed spectroscopically at high temperatures.

Three σ-bonds to phosphorus are readily formed, as suggested by the electronic structure, leading to stable derivatives PX_3, analogous to compounds of nitrogen NX_3. These compounds are pyramidal with bond angles somewhat greater than 90° but smaller than the tetrahedral bond angles of the corresponding nitrogen compounds, suggesting that hybridization to sp^3 orbitals is less important in phosphorus compounds.

Examples of multiple bonded compounds of phosphorus, analogous to those of carbon, nitrogen, or oxygen, are rare; in common with other second-row elements. Conditions for good overlap to form π-bonds, formed readily by $2p$ orbitals on adjacent atoms separated by $2p_\sigma$ bonds, are difficult to achieve for $3p$ orbitals separated by $3p_\sigma$ bonds. Many explanations for this effect have been suggested,[7] but most of the compounds described in the literature as containing multiple bonds to tervalent phosphorus are, in fact, polymeric materials.

The great majority of phosphorus compounds have four substituents arranged tetrahedrally around an sp^3 hybridized phosphorus atom. The fourth bond is derived formally by coordination of the non-bonding electrons of trivalent phosphorus with a Lewis acid; consequently the phosphorus atom bears a formal positive charge. When one of the substituents bears a negative charge, the bond to phosphorus is stabilized, a fact that is dramatically illustrated by the increased stability of carbanions when adjacent to tetrahedral phosphorus.

Undoubtedly an important factor in the chemistry of phosphorus compounds, particularly when compared with those of nitrogen, is the involvement of d orbitals. The special properties of tetrahedral phosphorus are believed to be the result of a degree of multiple bonding arising from the donation of non-bonding $2p$ electrons from a negatively-charged substituent into the vacant $3d$ orbitals of phosphorus.[8] There is substantial physical and chemical evidence for such bonding.[6] The resulting p_π–d_π bonds are considerably weaker than p_π–p_π bonds because of the relatively high energy and more diffuse nature of the $3d$ orbitals. The overlap of $2p_\pi$ orbitals is at a maximum when the two component orbitals are of similar type, giving strong bonding. For p_π–d_π bonding, however, the overlap integral increases with positive charge on the phosphorus atom and hence there is an unsymmetrical distribution of the bonding electrons, resulting in a strongly polarized bond ($\bar{P}$—$\bar{X}$). The high energy of formation (410 kJ mol^{-1}) of the phosphoryl bond (P—O), which is the driving force for many reactions of phosphorus compounds, is attributed to the formation of a second p_π–d_π bond at right angles to the first. The two lone-pairs on oxygen overlap with two separate $3d$ orbitals at phosphorus to give the symmetry of a triple-bond.*

Since tetrahedral phosphorus can accept electrons from negatively-charged substituents, clearly the possibility exists for phosphorus to form quinquecovalent compounds with five groups attached to phosphorus. Many examples of these penta-coordinate compounds are known, although the exact nature of the bonding is controversial.[9] However, the majority of these compounds possess the trigonal-bipyramidal configuration expected for compounds using sp^3d hybridized orbitals at phosphorus and they have the predicted longer axial bonds (see Chapter 10.6).

The addition of a sixth ligand to a quinquecovalent compound having five ligands is a reasonable possibility since no further promotional energy is required. Many hexa-coordinate phosphorus anions having the octahedral configurations expected for sp^3d^2 hybridization are known (Section 10.6.6).

10.1.2 NOMENCLATURE

The naming of phosphorus compounds is a most frustrating exercise for most chemists. Much of the confusion relates to the extensive use of trivial names, particularly of the

* For convenience the phosphoryl and thiophosphoryl bonds will be represented as P=O and P=S throughout Part 10.

phosphorus acids and their esters, some of which are prone to tautomerism. One needs to take great care when searching the older literature. For example, the compound $R_2P(O)OH$ is variously called dialkylphosphinic acid and dialkylphosphonic acid,[10] dialkylphosphonous acid in early British literature, and dialkylphosphinous acid in Beilstein.

Nomenclature, however, has become manageable since the publication of Rules[11] agreed between committees of the Chemical Society and the American Chemical Society. A summary of the more important points is presented in Table 1.

TABLE 1

Nomenclature of Organophosphorus Compounds

R_3P trialkylphosphine R_3PO trialkylphosphine oxide

Tervalent acids

phosphorous $[(HO)_3P]$ *derivatives*

$(RO)_3P$ trialkyl phosphite
$(R_2N)_3P$ hexa-alkylphosphorous triamide[a]
$(RO)_2PCl$ dialkyl phosphorochloridite
$ROPCl_2$ alkyl phosphorodichloridate
$(HO)_2PSH$ phosphorothious acid
$(R^1O)_2PSR^2$ *S*-alkyl *O,O*-dialkyl phosphorothioate

phosphinous (H_2POH) *derivatives*

$R^1_2POR^2$ alkyl dialkylphosphinite
R^1_2PCl dialkylphosphinous chloride[a]
$R^1_2PSR^2$ alkyl dialkylphosphinothioite
$R^1_2PNR^2_2$ *N,N*-dialkyl dialkylphosphinous amide

phosphonous $[HP(OH)_2]$ *derivatives*

$R^1P(OR^2)_2$ dialkyl alkylphosphonite
$RPCl_2$ alkylphosphonous dichloride[a]
$RP(SH)OH$ alkylphosphonothious acid

Quinquevalent acids

phosphoric acid $[(HO)_3PO]$ *derivatives*

$(RO)_3PO$ trialkyl phosphate
$(R_2N)_3PO$ hexa-alkylphosphoric triamide
$(RO)_2POCl$ dialkyl phosphorochloridate
$(RO)POCl_2$ alkyl phosphorodichloridate
$(R^1O)_2PONR^2_2$ *N,N*-dialkyl dialkylphosphoramidate
$(RO)_2P(O)SR$ *S*-alkyl *O,O*-dialkyl phosphorothiolate

phosphinic acid $[H_2P(O)OH]$ *derivatives*

$R^1_2P(O)OR^2$ alkyl dialkylphosphinate
$R_2P(O)NH_2$ dialkylphosphinic amide
$R_2P(O)SH$ dialkylphosphinothiolic acid
$R_2P(S)SH$ dialkylphosphinodithioic acid
R_2PSCl dialkylphosphinothioic chloride

phosphonic acid $[HPO(OH)_2]$ *derivatives*

$(R^1O)_2P(O)R^2$ dialkyl alkylphosphonate
$(R^1_2N)P(O)R^2$ *N,N*-tetra-alkyl alkylphosphonic diamide
$(R^1O)R^2P(O)F$ alkyl alkylphosphonofluoridate
$(R^1O)R^2P(O)SR^2$ *O*-alkyl *S*-alkyl alkylphosphonothioate

Phosphoranes

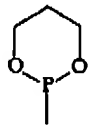
X_5P pentahalophosphorane
$R_3P{=}NH$ iminotrialkylphosphorane
$R_3P{=}CR$ alkylidenetrialkylphosphorane

Rings[b]

phosphetan

phospholan

phosphorinan



1,3,2-dioxaphosphorinan

[a] Such compounds are frequently named, more conveniently, as phosphine derivatives, e.g. Ph_2PCl chloridiphenylphosphine, $(Me_2N)_3P$ tris(dimethylamino)phosphine.

[b] Under IUPAC rules a terminal 'e' is added, to give phosphetane, *etc.*

10.5

Phosphoric Acid Derivatives

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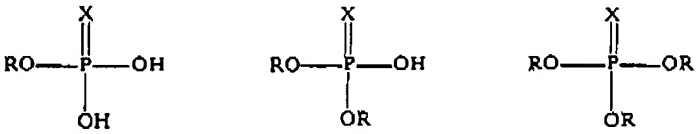
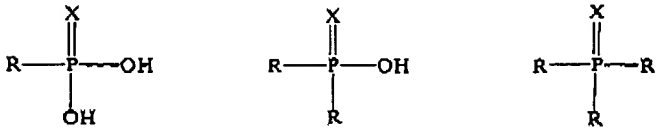
This chapter describes the chemistry of tetra-coordinate phosphorus compounds possessing the phosphoryl (P=O) bond or the corresponding bond between phosphorus and sulphur; comparatively few compounds are known in which the phosphorus is similarly bonded to selenium or tellurium. In principle, all of these compounds may be considered as being derived from orthophosphoric acid. (a) By successive replacement of hydrogen atoms by organic groups, monosubstituted dihydrogen phosphates (**1**; X = O), disubstituted monohydrogen phosphates (**2**; X = O), and finally phosphate triesters (**3**; X = O are obtained. (b) Replacement of the OH function by halogen gives acid halides, and replacement by nitrogen-containing groups gives, for example, amides. (c) One or more oxygen atoms may be replaced by sulphur (*e.g.* **1–3**; X = S) or selenium (*e.g.* **1–3**; X = Se) to form thio- or seleno-phosphoric acid derivatives. Finally, (d) the replacement of complete OH groups by organic groups leads successively to phosphonic acids (**4**; X = O), phosphinic acids (**5**; X = O), and ultimately to tertiary phosphine oxides (sulphides, *etc.*) (**6**; X = O or S).

Superficially, the phosphoryl and carbonyl bonds may seem to resemble each other. Both bonds are highly polar, in the sense $M\overset{\delta+}{-}\overset{\delta-}{O}$ (M is C or P), and the resultant strong electron-withdrawing ability of each bond confers a high degree of mobility on hydrogen

attached to adjacent atoms. In the case of the phosphoryl bond, as for example in some phosphonic and phosphinic acid derivatives, and even in some phosphine oxides, such

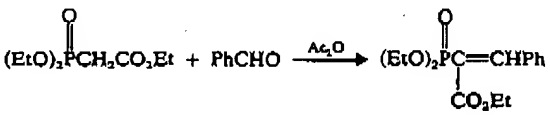


(1) (2) (3)



(4) (5) (6)

α-CH groups are activated particularly strongly when situated between two phosphoryl groups, or between phosphoryl and carbonyl or aryl groups. Indeed, phosphoryl methylene compounds very often behave like conventional active methylene compounds (equation 1).[1]



(1)

Carbonyl and phosphoryl bonds are both clearly detectable spectroscopically in the infrared region: the phosphoryl bond absorbs strongly within the overall range 1390–1080 cm^{-1}, the exact position of absorption being dependent upon the nature of the attached groups in association with their steric and electronic effects.[2,3] However, the resemblance between phosphoryl (P=O) and carbonyl (C=O) bonds ends there. Because of differences in hybridization at the carbonyl carbon (planar sp^2) and phosphoryl phosphorus (tetrahedral sp^3) atoms, the two bonds are affected by the total electronic effect of attached groups to different extents, the carbonyl group by a combination of inductive and mesomeric effects, the phosphoryl group by the inductive effect only. In addition, because of the marked contrast in molecular geometry around the two bonds, differences in the degree of steric interaction by attached groups also become apparent. Changes in the relative rates of hydrolysis of carbonyl and phosphoryl chlorides with variation of attached groups provide good evidence for differences in the combined steric and electronic effects at the two reactive sites.[4–7]

The thiophosphoryl (P=S) bond is much less polar but more polarizable than the phosphoryl group, and in the infrared region is characterized by a greater variation in intensity of absorption, and also in the absorption frequency, this lying generally within the range 580–850 cm^{-1}; the infrared technique is thus of less value for diagnostic purposes than in the case of the phosphoryl bond.[2,3]

Although once thought to be relatively inert, the phosphoryl bond is now believed to participate directly in numerous chemical reactions. Thus it can act as an electron donor, and as such can be protonated on oxygen, the relative basicities of the phosphoryl group in a series of compounds being measurable using ^1H and ^{31}P n.m.r. spectroscopy.[8] The phosphoryl bond also complexes with metallic salts and electron acceptors such as boron trifluoride. The P=O bond is seen, therefore, to exhibit nucleophilic character, and although this will be considered more fully at a later stage, two examples may now be quoted showing the involvement of the phosphoryl group in reactions under particularly mild conditions (Scheme 1). Thus oxidation of the phosphines (7) by potassium permanganate in acid solution yields the spirophosphoranes (9), probably *via* the phosphine oxides

PATENT
2801-0155p

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: Susan M. DALUGE et al

Appl. No.: 08/957,045 Group: 1624

Filed: October 24, 1997 Examiner: M. Berch

For: CHLOROPYRIMIDINE INTERMEDIATES

DECLARATION UNDER 37 C.F.R. §1.132

Honorable Commissioner for Patents
Washington, DC 20231

April 23, 2001

Sir:

I, Dr. Susan M. Daluge, hereby declare as follows:

I am an inventor of the above-identified application Serial No. 08/957,045 filed October 24, 1997.

I received a Ph.D degree in Organic Chemistry from the University of Minnesota Chemistry Department in 1969. I am a Principal Scientist in the Department of Medicinal Chemistry at Glaxo Wellcome, Inc.

I have studied the specification and I am familiar with this field of technology. I have received an American Chemical Society award for this chemistry.

I am intimately aware of the process disclosed in Daluge '697 (U.S. Patent 5,087,697), because I am also an inventor of Daluge '697. The Examiner has used Daluge '697 as the primary reference in the outstanding Office Action in a 35 U.S.C. §103(a) rejection. I now remark on the Examiner's rejection of the claims as being obvious over the cited prior art.

Protecting Group R^3 on Compounds of Examples 25-27 in Daluge '697

The present inventive process has significant advantages over the process of Daluge '697. Moreover, the Daluge '697 process has clear disadvantages. A synthetic scheme depicting Route 1 and Route 2 of Daluge '697 and the present invention is attached to this Declaration. Daluge '697 discloses a "research route", which is useful only to synthesize a few grams of the material; thus, the process is not useful for manufacturing of a drug, because of the complex mixtures formed. Examples 25-28 and Examples 3-4 are prepared only on a gram scale.

Chlorination of di-oxopyrimidine without blocking the amino groups with acyl groups results in tars and low yields. A tar coats the reactor, which means the process step cannot be scaled up. A tedious chromatography step is required for purification to get a low yield. To avoid these problems, Daluge '697 Route 1 blocks the amino group at the 2-position with isobutyric acid to make the purine.

The compound of Example 27 has a protecting group on the 2-amino position of the purine. The 6-chloropurine intermediate was not isolated in Example 27 because treatment with aqueous acid to remove the isobutryl group from the 2-position causes hydrolysis of the 6-chloro group to 6-oxopurine, lowering the yield. Instead, the crude mixture containing 6-chloropurines was subjected to reaction with cyclopropylamine and the resulting mixture (glass which could not be solidified) was then

chromatographed in order to isolate 53% of the desired 6-cyclopropylaminopurine on a gram scale after a difficult separation (large volumes of solvent, many fractions, and a high ratio of silica gel to compound required) from the compound in which the isobutryl group had been removed (partial removal during cyclopropanation). Example 28 is the deprotection step of the title compound of Example 27. The final product in Example 28 after another chromatography purification necessitated by the noncrystalline nature of the product (i.e. could not be solidified to purify) results in an 80% yield.

Examples 3 and 4 in Daluge '697

The compound in Example 3 of Daluge '697 is a triaminopyrimidine, which is not suitable for a large-scale process. The compound is air sensitive, light sensitive, heat sensitive, and chelates metals (undesirable, potentially toxic impurities in final drug resulting). The compound is a dark oil that could not be solidified to effect purification. Extensive chromatography was necessary to obtain a solid with sufficient purity to enable use as an intermediate for synthesis of final cyclopropylaminopurine. Once purified, the compound must be stored in a dark cold inert atmosphere, which is a problem in a scale-up process plant.

Example 4 in Daluge '697 describes a very difficult reaction with following work-up. Example 4 uses diethoxymethyl acetate instead of trialkylorthoformate. The complex mixture of products

from the procedure disclosed in Example 4 was purified by chromatography to produce a 46% yield of the final product on a gram scale.

Summary of the Process of the Present Invention versus the Process of Daluge '697

The process of the present invention uses a trialkylorthoformate in the presence of aqueous acid to cause ring formation of the purine. A protection group is not needed on the 2-position amine to give good yield. This was unexpected.

The attached synthetic route of the present invention shows Compounds of formula III, which are achieved in high yield and purity. The previous synthetic step uses transient blocking during chlorination to avoid the tars; thus, the compounds are purified by simple precipitation. This reaction is done on thousands of kilogram scale. Compounds of formula (III) are more reactive to amines; thus, a shorter reaction time is needed.

Compounds of formula VI are much improved over the compound of Example 3, because they are not air sensitive, light sensitive or heat sensitive. They are solids purified by precipitation. It is such a clean reaction typically the compound does not require purification. Compounds of formula VI do not chelate metals and are stable indefinitely at room temperature.

Compounds of formula VII are formed cleanly from compounds of formula VI and are isolated by precipitation. An unexpected part of the synthesis is that the CHO of formula VI is removed

during the formation of formula VII. This was discovered by ^{13}C-label of the formyl group in formula VI.

Conclusion

A significant difference exists between the process of the present invention and the process as described in Daluge '697. In Daluge '697 and the other cited prior art the reaction steps lead to impurities and difficult purification steps. Therefore, the synthetic routes described in Daluge '697 produce the compounds in Example 4 and 28 at lower yields and purity; thus, these process steps are not useful in a large scale manufacturing process. The process of the present invention is unexpectedly superior to the processes of Daluge '697.

The CHO group in the compounds of formula (III) provides for the improved physical properties of the compounds of formula (VI). Therefore, the final products of formula (VII) are clean and suitable for drug synthesis.

The above statements show that side-reactions persist in the process of Daluge '697 without protecting groups and the present process unexpectedly has superior results without the need for a deprotection step near the end of the total synthetic pathway.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both,

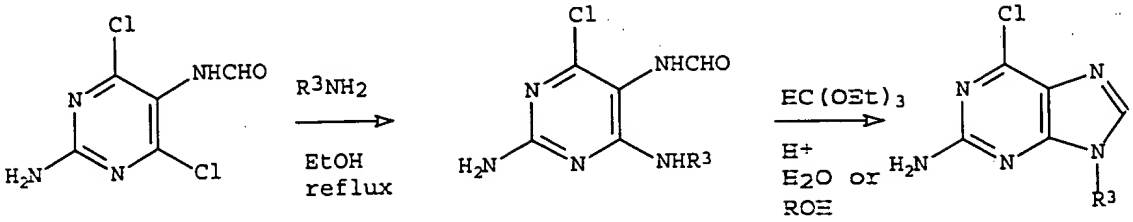
under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

April 27, 2001
Date

By: Susan M. Daluge
Dr. Susan M. Daluge

Attachment to 37 C.F.R. §1.132 Declaration

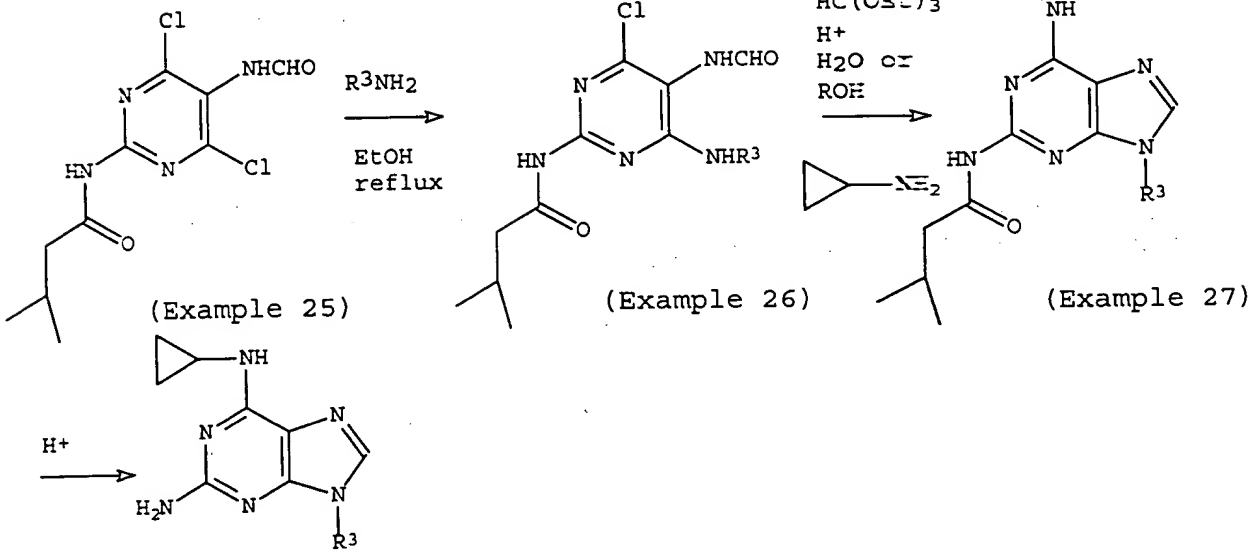
Present Inventive Process



(III) (VI) (VII)

Daluge '697 Processes

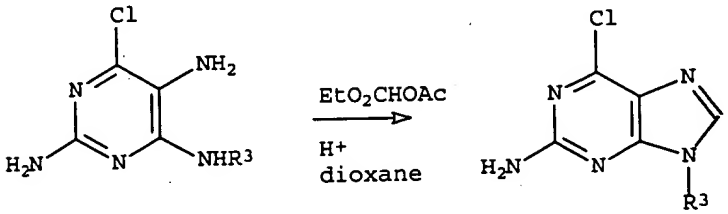
Route 1



(Example 25) (Example 26) (Example 27)

(Example 28)

Route 2



(Example 3) (Example 4)